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A Hard Scientific Quest: Understanding Voluntary Movements

Emilio Bizzi & Robert Ajemian

Abstract: In this article we explore the complexities of what goes on in the brain when one wishes to perform even the simplest everyday movements. In doing so, we describe experiments indicating that the spinal cord interneurons are organized in functional modules and that each module activates a distinct set of muscles. Through these modules the central nervous system has found a simple solution to controlling the large number of muscle fibers active even during the execution of the simplest action. We also explore the many different neural signals that contribute to pattern formations, including afferent information from the limbs and information of motor memories.

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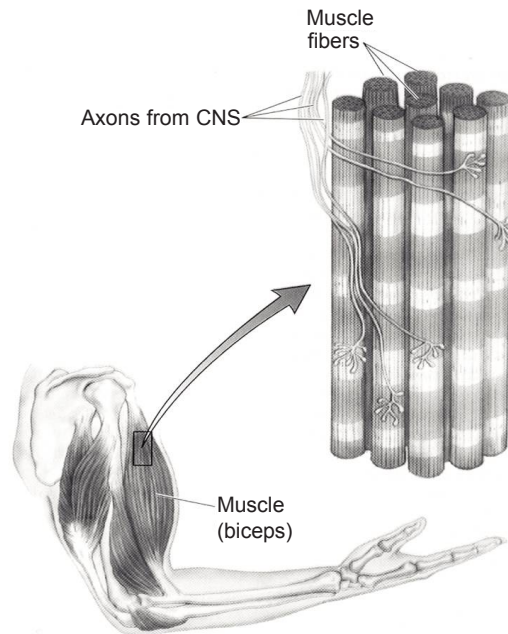
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Scientists and nonscientists alike rarely stop to consider what is going on in their brains when they perform a voluntary movement such as reaching for an object, throwing a ball, or driving a car. Why? Presumably they may realize that translating something as evanescent as a wish to move into muscle contractions must be an awfully complicated process. Indeed, they are right: the neural processes that subserve even the simplest everyday actions are incredibly complex and only partially understood. In this essay we take up the challenge of explaining what we know about this fascinating and complex topic.

Let us begin with the basic fact that, in general, our movements – even the simplest actions – are accomplished through activation of a large number of muscles. For example, if you are sitting at your desk typing at your computer and decide to turn to pick up a cup of coffee, you will activate, approximately at the same time, the eye muscles, the numerous muscles in the neck, and the muscles of the shoulder, arm, forearm, and fingers. A simple computation would show that your brain has activated at least thirty muscles. But note that each muscle is made up of cells called muscle fibers, and that each muscle fiber receives a neural input via its own nerve fiber (see Figure 1). It follows that the number of elements

Figure 1
Muscle Fibers and Axons from Motor Neurons



Axons are the long threadlike part of a nerve cell along which impulses are conducted from the cell body to other cells. Source: *Frontiere Della Vita* (Rome: Istituto Della Enciclopedia Italiana, 1999).

controlled by the neural motor system is very large, even during simple movements.

Imagine now what must be taking place in the brain of an athlete in the heat of a soccer match, when practically all the muscles of the body must be precisely coordinated, with little time for preplanning. Clearly, the soccer player trying to score a goal has neither the time nor the inclination to explicitly formulate the command signals to control the millions and millions of muscle fibers in his or her body, and must instead rely on an effective simplifying strategy. How our brains cope with this inherent complexity remains one of the fundamental questions in motor system neuroscience.

Years ago a group of neuroscientists, including one of the authors of this essay, decided to investigate this basic question by launching a series of exploratory searches aimed at identifying the way in which the central nervous system (CNS; the complex of nerve tissues that control the activities of the body, comprising the brain and the spinal cord) controls the multitude of muscle fibers that are activated during movements.¹ We started by focusing on the spinal cord in lower vertebrates and quickly found that a special group of cells called interneurons – neurons that transmit impulses between other neurons, and that are interposed between the sensory portion of the spinal cord and its motor output – are the key elements that implement the simplifying strategy.²

Interneurons are organized in functional modules, and each module activates a particular set of muscles in distinct proportions. We labeled this entity of patterned muscle activation a *muscle synergy*. This modular spinal structure is the central piece of a discrete combinatorial system that utilizes a finite number of discrete elements (that is, the muscle synergies) to express a voluntary movement. The combinatorial system is controlled by the neurons residing in the cortical frontal areas (the cerebral cortex covering the frontal lobe). Anatomically, the cortical neurons transmit impulses to select and combine spinal modules. Following the arrival of cortical command signals, a cascade of neural events ensues: the activated spinal modules fire the motoneurons (nerve cells forming part of a pathway along which impulses pass from spinal cord to a muscle) and their motor nerves induce a depolarization of the muscle fibers, which in turn is followed by muscle contraction and movements. Researchers can easily record the electromyographic activity (EMG) – the depolarization of muscle fibers – with electrodes placed in or on the muscle surface.

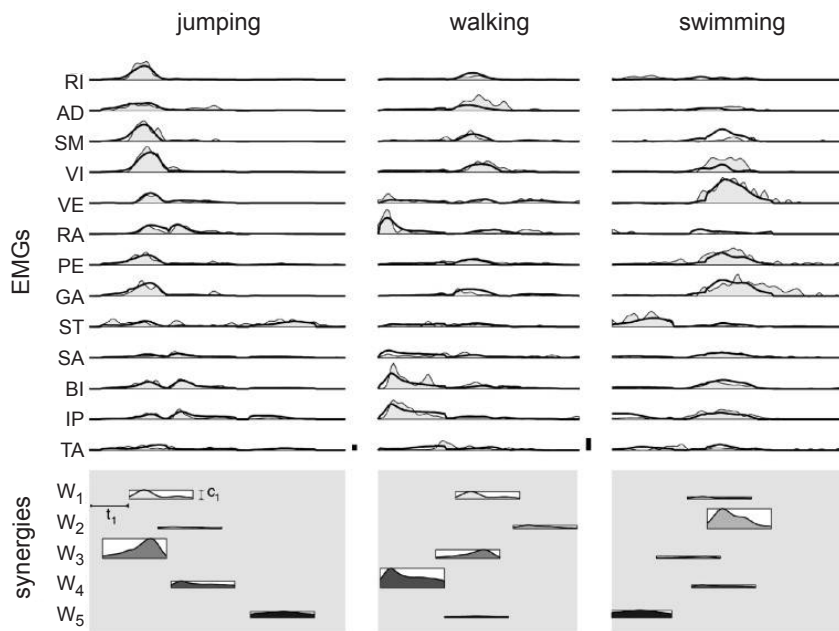
To identify the muscle synergies we used a factorization algorithm that takes as input all of the muscle EMG data and extracts from these data both a set of generative muscle synergies and a coefficient of each synergy during the composition of a particular motor behavior. The experimental evidence supporting the idea that the CNS uses muscle synergies as output modules is illustrated in Figure 2. This illustration shows that a small number of synergies explain a large fraction in the variation of muscle patterns. In other words, not as many individual muscle functions need to be controlled as one might have initially thought.

Figure 2 shows the EMG records for frogs that are jumping, walking, and swimming.

The upper (unshaded) section of Figure 2 lists the names and the EMGs of thirteen leg muscles. The shaded wave areas in this section of the figure represent the rectified, filtered, and integrated EMGs recorded during the execution of a single instance of jumping, walking, and swimming movement. The thick line defining the contour of the wave represents the outcome of a computation that reconstructs the muscle patterns by utilizing the muscle synergies extracted by the factorization procedure. The lower (shaded) section of Figure 2 shows the coefficients of the five synergies that were found through the factorization. The coefficients are placed in a rectangular box whose width corresponds with synergy duration; their position indicates onset delay and the height represents amplitude of EMG. Figure 2 demonstrates two important points: 1) the same synergies are found to contribute to different movements (note that synergies W_1 , W_3 , and W_4 are a constituent of both jumping and walking, but with different coefficients of activation of EMGs; the synergy W_5 is used in both jumping and swimming); and 2) different behaviors may be constructed by linearly combining the same synergies with different timing and scaling factors. Recent results from the study of muscle patterns during a variety of movements in humans, monkeys, and other vertebrates have shown that combining a small set of muscle synergies appears to be a general strategy that the CNS utilizes for simplifying the control of limb movements.

The specific factorization algorithm that we used to extract the underlying synergies from the overall EMG data set is known as the nonnegative matrix factorization.³ Other factorization algorithms could have been used, such as the popular principal component analysis (PCA); but neuroscientist Matt Tresch and his colleagues have shown that whatever technique one uses to identify the synergies, the end results are

Figure 2
Synergies and Variations of Muscle Patterns



The main muscles of synergy W_1 are RI, AD, PE, and GA. The main muscles of synergy W_2 are SM, VE, PE, and GA. The main muscles of synergy W_3 are RI, SM, and VI. The main muscles of synergy W_4 are RA, BI, and IP. The main muscles of Synergy W_5 are ST and IP. These synergies were extracted by pooling together the EMGs of three frogs during jumping, walking, and swimming movements. Source: Emilio Bizzi, Vincent C. K. Cheung, Andrea d'Avella, Philippe Saltiel, and Matthew Tresch, "Combining Modules for Movement," *Brain Research Reviews* 57 (2008): 125–133.

essentially the same.⁴ This suggests that the observed muscle synergies are real, as opposed to an artifact of the data analysis. Additional observations corroborate the independent physiological existence of muscle synergies as fundamental and irreducible units of motor control that are linearly combined to generate movement.⁵

The experimental evidence described above indicates that the peripheral sections of the motor system operate as a discrete combinatorial system. In a way, then, the motor system is like language, a system in which discrete elements and a set of rules for combining them can generate a large number of meaningful entities that are dis-

tinct from those of their elements. Thus, we may have solved the problem of how the motor system copes with having to control so many different muscles and motor units during the course of a movement: it does so through intelligent modularization at the level of the spinal cord.

But having proposed a solution for one problem, we are immediately led to another: how does the brain figure out the correct combinations of synergies that are required to execute a motor act? Certainly, what is impressive about the motor system is its capacity to find original motor solutions to an infinite set of ever-changing circumstances. This capacity is entirely de-

pendent upon the computations performed by neural circuitries of the cortical areas of the frontal lobe (the lobes on each cerebral hemisphere lying immediately behind the forehead). These cortical areas generate signals that combine, select, and activate the spinal modules. Understanding these computations has been the main goal of neuroscientists, neurologists, and psychologists involved in the study of motor control. Some progress toward this goal has been made, but as we will discuss, many of the hard questions remain unanswered.

Our description of the way in which cortical commands generate patterns of activity for activating the spinal cord modules will begin by considering the major inputs and outputs of the motor cortical regions.

In each frontal lobe hemisphere, there are at least four major regions concerned with generating signals for voluntary movements: the dorsal and ventral premotors (the cortical areas in front of the motor cortex), the supplementary motor area, and the primary motor cortex.⁶ These highly interconnected regions receive diverse modalities of information (inputs) from a variety of sources, including: 1) external sensory information about the state of the world (such as visual, auditory, tactile information); 2) internal sensory information about the state of the body (such as muscle length and tendon force); 3) the executive attentional system for determining behavioral saliency; and 4) inputs from major subcortical areas such as the cerebellum and the basal ganglia (whose roles in motor control are somewhat obscure). These signals are conveyed to the motor cortical areas where they connect to the dendritic tufts of the large output cells of the cortical layers 5 and 6 (see Figure 3).⁷ There these signals are somehow integrated into a coherent unit to set up a neuronal depolarization, which

is conveyed via the dendritic tree to the cell body of the big output cells in layer 5, and from there via long pathways to the spinal cord.

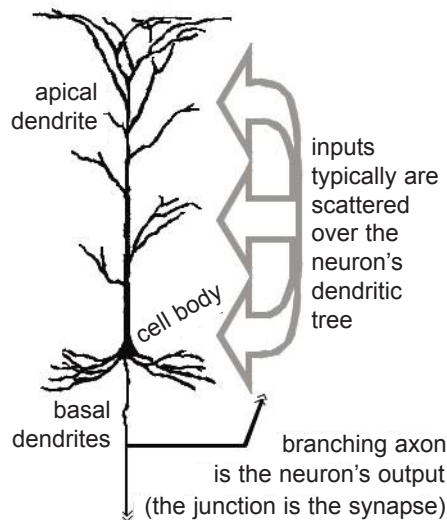
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There are a variety of output pathways made of axons of cortical layers 5 and 6 that connect premotor and primary motor cortical areas with a different class of spinal neurons. One of these descending pathways conveys information about an impending movement, an observation suggesting that it may be part of a cortico-spinal circuit contributing to an early shaping of motor commands. Additional output pathways include: 1) cortico-spinal fibers terminating at the level of the interneurons, which activate the spinal cord modules and therefore are responsible for the expression of the muscle synergies;⁸ 2) a cortico-motoneuronal pathway from the most caudal sections of the primary motor cortex,⁹ though we do not yet know how these two descending sets of fibers cooperate in the execution of voluntary movements; 3) an important set of fibers connecting the motor cortex to the basal ganglia; and 4) a set of fibers connecting the cortex to the cerebellum in the recurrent loop, which create a cerebellar pathway whose complex function is possibly related to reentry circuits that contribute to shaping the construction of cortical patterns of activity. (The function of the cerebellum has long been a source of debate possibly relating to the function of cortical patterns activity; see Figure 4.)

But also critical is that the descending pathways are mirrored by ascending sets of fibers forming numerous reentry circuits. Thus, the intimate ties between the cortex and the periphery are an essential feature of the “system” for movement.

There is a vast amount of data indicating that the motor cortex plays a central role in generating motor behavior, but there is lack of consensus on how neural process-

Figure 3
Pyramidal Neuron



Source: *Frontiere Della Vita* (Rome: Istituto Della Enciclopedia Italiana, 1999).

ing within the cortical areas of the frontal lobe contribute to voluntary movements. An approach to interpret cortex neural activity, first introduced by Edward Evarts at the National Institutes of Health, was based on recording the activity of single cortical neurons in monkeys and then correlating their firing rate with joint motion, force, and limb posture.¹⁰ Evarts concluded that the motor cortical neurons likely encoded the muscular force that is needed for movement. In the early 1980s, neuroscientist Apostolos Georgopoulos, using a modified behavioral setup, showed that cortical neurons recorded from the primary motor cortex were broadly tuned to the direction of hand movements.¹¹ This correlation suggests that the motor cortex encodes high-level parameters of movement such as direction in task space, rather than low-level parameters such as muscle forces. But the story did not end there. In the last few decades, researchers have

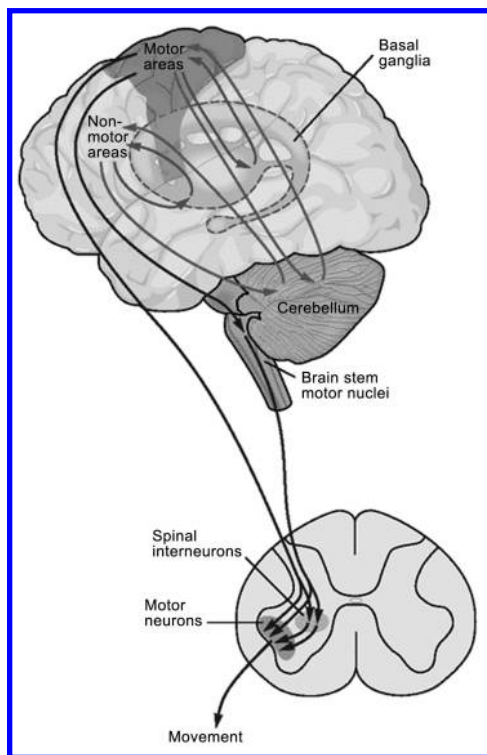
implicated the motor cortex in the encoding of a litany of different movement variables, including hand velocity, hand position, joint angles, joint torques, movement sequence information, and movement curvature. Further, the response properties appear nonstationary, changing with behavioral contexts and choice of task.¹² So what does this all mean? What does the motor cortex really do?

To put all these observations in perspective, we should consider the limitations of microelectrode recordings. In acute recording, one or a handful of neurons are recorded. In chronic recording, an array of electrodes is implanted that can record from roughly one hundred neurons simultaneously. Yet there are millions of neurons in the motor cortices, each one highly interconnected to other motor cortical neurons and to the many input sources that project to it. The endeavor is thus lim-

Figure 4

The Cortex, Cerebellum, Brain Stem, and a Section through the Spinal Cord

Emilio
Bizzi &
Robert
Ajemian



The motor cortical areas are shown with some of the fibers connecting it to the basal ganglia and the cerebellum. Two cortical spinal pathways are shown, one a direct pathway from the cortex to the spinal motoneurons and another connecting the motor cortex to the spinal interneurons. Source: Eric R. Kandel, James H. Schwartz, and Thomas M. Jessell, eds., *Principles of Neural Science*, 4th ed. (New York: McGraw-Hill, 2000).

ited both by problems of undersampling (you are only recording from a tiny fraction of a population) and problems of limited sampling information (usually you do not know in what layer a recorded neuron resides, meaning you do not know where in the context of this complicated and highly distributed circuit your neuron fits). An analogy: suppose that you know nothing about how computers work, but are asked to figure it out by sticking a volt meter into different regions of a computer while it runs various programs, recording its electric potential. Considering this challenge, perhaps it is not so surprising that the manner in which patterns form at the

output layer of the motor cortex to generate movements remains a mystery.

Clearly, to move our understanding of the motor cortex forward, new approaches are needed. In the last few years, prompted by the urge to look for new avenues, neurophysiologists and computational neuroscientists have joined forces in order to make sense of the neuronal recording data and then generate theories and models of the motor cortex. The most notable proposed models, such as optimal feedback control and recurrent neural network, are attempts at formulating a comprehensive motor control theory;¹³ but because their focus is based on our limited knowl-

edge of neurons, the resulting models had only a modest impact on the field. In general, these models failed to consider the complex interactions among different classes of cortical cells and the role of the recurrent circuits that link the cortex with the spinal cord, basal ganglia, and cerebellum. The cortical neurons' activity should have been evaluated in a different way, since these cells belong to an ensemble.

Fortunately, thanks to developments in molecular biology, a panoply of new techniques is becoming available. For example, imaging techniques are being developed that will enable an experimenter to record from thousands of neurons simultaneously, while at the same time monitoring the anatomical changes taking place within the circuit at the synaptic level. Different strains of viruses carrying channelrhodopsin into targeted populations of neurons now make it possible to activate/inhibit neural circuitry. This is an important development because neural circuits are inherently parallel and highly interconnected, meaning that it is difficult to understand what one part of the circuit is doing in isolation of the rest of the circuit. Such technological breakthroughs, together with the development of mathematical tools for processing and modeling high-dimensional distributed dynamical systems, may change the playing field in systems neuroscience in the years to come.

Neuronal activity in the motor cortical areas is a complex function of sensory inputs, regional and local interactions among cells, and cortical reentry circuits. In addition, recent investigations have established that one more significant way to fire the cortical neurons is just to image an action without producing an actual movement. There is also evidence that shifting from one mental task to another changes the pattern of brain activation. These results were obtained by monitoring region-

al blood flow either with a positron emission tomograph or fMRI (functional magnetic resonance imaging). It is of interest that most of the activation was found in the premotor and supplementary areas, but less so for the primary cortex for both motor imagery as well as movement observation. These findings show that the deliberate representations of actions involve activation similar to those occurring during voluntary movements. These observations are important as they expand the scope of the motor system beyond the generation of actions. Imaging the brain during a motor action means to evaluate the consequence of self-programmed movements before execution, while also providing ways to represent other people's actions.

As a consequence of the intense exploration of the motor imaging underlying physiology is the realization that cells in the premotor and primary motor cortex are active when a subject plans an action. This finding has opened the way to record from the human cortex and utilize the neural signals for prosthetic devices.

Closely linked to the motor imaging of actions is the brain's representation of motor memories; that is, when we learn a skill, how is that skill represented in our neural circuits? Since most of what we do is guided by what we have learned, this capacity for motor learning embodies a crucial facet of our existence. Imagine how difficult life would become if every time we engaged in a routine act, like tying our shoes, we had to perform it with the skill level of a novice. Instead, as we go through life we gain facility and acquire expertise in the form of motor memories: memories of how to perform skilled motor acts. Where are these motor memories stored and how are they represented?

In the case of computers, we know where and how information is stored. It is stored in the digital switches of transistors that

are housed and addressed in specific locations within the computer (the hard drive or random-access memory) or various external digital media (such as a disk). In the case of human declarative memory – which, loosely, is factual information about one’s life (names, places, events, and so on) – we also have a fairly good idea. Declarative memory is stored in the medial temporal lobe of the brain (a region of the cerebral cortex that is located beneath the lateral fissure on both cerebral hemispheres of the mammalian brain) including the hippocampus (the elongated ridges on the floor of each lateral ventricle of the brain, thought to be the center of emotion, memory, and the autonomic nervous system), the entorhinal cortex (an area of the brain located in the medial temporal lobe that functions as a hub in a widespread network for memory and navigation), and perirhinal cortex (a region of the medial temporal lobe of the brain that receives highly processed sensory information from all sensory regions, and is generally accepted to be an important region for memory). Motor memory, on the other hand, appears to be broadly distributed across all of the major components of the motor circuit, including the motor cortices, the cerebellum, and the basal ganglia; and how motor memories are stored still remains murky, though we have clues.

One clue has come from force field studies in which monkeys adapted their reaching movements to different environments and perturbations while the activity of single neurons in their motor cortices was recorded.¹⁴ As expected, when a monkey learned to move in a novel context, the activity patterns of the recorded neurons changed. This finding is generally consistent with the synaptic trace theory of memory, which says that memories are embodied in patterns of synaptic connections (synapses are the junctions between two nerve cells consisting of a minute gap

across which impulses pass by diffusion of a neurotransmitter) that change in an experience-dependent fashion, such that after the experience, the circuit is capable of generating a new output. However, it was unexpectedly found that some of the neurons maintained their altered activity patterns even when the animal stopped performing the new task and returned to the original task. Further, as the behavior switched from one task to another, the pattern of activity of the neurons changed in an unpredictable fashion.

In a similar vein, a pair of studies used the technique of two-photon microscopy to study anatomical changes in the synaptic connectivity of the mouse motor cortex during the learning of new motor skills.¹⁵ This remarkable technology allows experimenters to visualize individual synaptic spines, the smallest unit of information transmission in the brain, over periods of weeks or months. As expected, these studies showed that learning is indeed accompanied by the formation of new synaptic spines. However, these studies showed something else that was unexpected, even shocking: when the animals are not learning anything, the synaptic spines are still turning over at a high rate. In fact, the rate of turnover is so high in the baseline conditions that most of the new spines created during the formation of the new memory will be gone in a matter of months or, at most, a couple of years. Yet these same motor memories are known to persist for the animal’s entire life.

These observations lead to a profound paradox. If we believe that memories are made of patterns of synaptic connections sculpted by experience, and if we know, behaviorally, that motor memories last a lifetime, then how can we explain the fact that individual synaptic spines are constantly turning over and that aggregate synaptic strengths are constantly fluctuating? How can the memories outlast their puta-

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tive constitutive components? This is currently one of the great mysteries in motor neuroscience and, in fact, all of systems neuroscience, reinforced by the dozens of two-photon microscopy studies that have found that regardless of which region of the cortex is examined, the synapses are constantly turning over. How is the permanence of memory constructed from the evanescence of synaptic spines?

In an attempt to answer this question, we recently developed a new type of neural network with the distinguishing feature of synapses that are constantly changing even when no learning is taking place.¹⁶ We showed that under certain conditions – conditions that hold during motor learning – the network can stably learn a variety of skills despite these constant weight changes. The basic point of the model is to reexamine the notion of what constitutes a memory. Neural circuits are highly redundant in that there are many more synapses than there are neurons, with each neuron being contacted, on average, by ten thousand synaptic spines. Thus, within a neural circuit, many different configurations of synapses can give rise to the same input-output processing. In other words, a network can perform the same function even if its synapses undergo change. With this in mind, we suggest that a memory, instead of being composed by a fixed pattern of synaptic weights, is actually embodied by a fixed pattern of input/output processing at the level of neural activities. This flexibility gives the system some slack to accommodate synaptic turnover, an inevitable fact of cell biology, since synapses are made of proteins, which have short lifetimes. Models, like this one, that rely on the stochastic dynamics of complex systems may prove to be fertile territory for understanding recent and future data on synaptic dynamics.

A final question is whether models like ours can simultaneously shed light on both

the small-scale physiology/anatomy and the larger-scale behavior of a subject. After all, the ultimate goal of neuroscience is to mechanistically link the physical entity of the brain to the more ethereal phenomena of the mind. This is not always easy to do and often a model is constructed to explain data in one domain or the other, but not both. Here we have found that a model with perpetually fluctuating synaptic connections may explain an interesting result from the kinesiology and sports science community that has been known for over one hundred years.

The finding is called the warm-up decrement and it can be illustrated as follows: to function at a peak performance level, a professional athlete trained in a fine motor skill must practice or warm up for an extended period of time immediately prior to performing. For example, professional golfers and professional tennis players will practice for an hour or more before playing in a major competition. In a certain sense, this seems strange. These athletes have spent much of their lives practicing a particular skill, so why do they still need to practice for so long before competing? A robot that performs a skill needs only to be turned on and shortly thereafter it will execute the skill to the best of its abilities. So why do human experts need additional practice right before performance?

One possibility is that the practice is needed to warm up the athlete's muscles, ligaments, and tendons. However, this theory has been refuted by experiments in which the body is warmed up by other means, resulting in sub-peak performance. Further, athletes of all calibers widely accept that the warm-up ought to use the same skill set that will be used in performance. If a professional tennis player were to practice squash an hour before playing a tennis match, the results would be disastrous, though many of the same muscles are used in both activities. So what, then,

is going on during this period of warm-up? One explanation could be a need for continuous neural recalibration to optimize performance if, as proposed in our model, synapses are always changing. Thus, over time, there might be a slight drop-off in performance on the basis of synaptic turnover alone. For an expert who performs at the highest level, even a slight decrement in performance can be obvious and exploited by competition, thereby making practice immediately before an event required to fine-tune the network into a state of optimal performance.

Whether or not the proposed model is correct in its explanation remains to be determined. But what we know for sure is that the continued use of modern imaging technology to probe synaptic dynamics will provide crucial data in the years ahead to constrain and inform our efforts at understanding the neural processes that underlie motor learning.

In this review we have focused on the hard scientific questions involved in understanding the seemingly effortless generation of voluntary movements. With respect to the peripheral motor system (spinal cord and muscles), we have pointed out the many difficulties associated with controlling millions of muscle fibers partitioned across dozens of muscles, and described how, through spinal cord modularity, the CNS has found a simplifying solution. However, no answers have yet been found to explain how the cortical motor areas of the frontal lobe construct the spatiotemporal patterns of neural activity necessary to activate the spinal cord, enabling it to execute a specific movement. Certainly, we do know that high-level movement goals and attention-related signals are represented in the premotor areas and that the spread of these signals to the primary motor cortex, possibly already primed by afferent information about limb posture, will

somehow trigger the retrieval of motor memories and, subsequently, the formation of a signal to the spinal cord. But the detail of this complicated process, which critically involves coordinate and variable transformations from spatial movement goals to muscle activations, needs to be elaborated further. Phrased more fancifully, we have some idea as to the intricate design of the puppet and the puppet strings, but we lack insight into the mind of the puppeteer.

We have also discussed the hard problem of where and how motor memories are stored. This, too, is a difficult and unsolved problem, in large measure because of the highly distributed and interconnected nature of neural circuits. Based on first principles, we can be sure that memory storage in the brain, however it works, will differ radically from information storage in a computer. New computational paradigms may be needed to provide a greater understanding, and we have here briefly described one model that attempts to shift the paradigm based on our knowledge of perpetually fluctuating synapses.

On the face of it, investigating the problems of both pattern formation (for the purpose of control) in the motor cortex and motor memory storage in the aggregate motor circuit is going to be a daunting affair requiring the combined efforts of physiologists, molecular biologists, and computational neuroscientists. But as the history of science has shown, it is possible that nature might have developed some surprisingly simple and unexpected shortcuts that, if discovered, may go a long way toward providing the ultimate answers. After all, who would have guessed that a simple receptive field in the visual cortex might be the key to recognizing the complexities of a face?

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Bizzi &
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